

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A01N 25/08, 25/12, A61K 9/14		A1	(11) International Publication Number: WO 98/03064
			(43) International Publication Date: 29 January 1998 (29.01.98)
(21) International Application Number: PCT/US97/12183		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 15 July 1997 (15.07.97)		Published <i>With international search report.</i> <i>With amended claims and statement.</i>	
(30) Priority Data: 08/797,517 23 July 1996 (23.07.96) US 08/889,185 7 July 1997 (07.07.97) US			
(71) Applicant: FMC CORPORATION [US/US]; 1735 Market Street, Philadelphia, PA 19103 (US).			
(72) Inventor: SULLIVAN, Edward, K.; 26 Beech Street, Stanhope, NJ 07874 (US).			
(74) Agent: CALDWELL, John, W.; Woodcock Washburn Kurtz Mackiewicz & Norris, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).			
(54) Title: DISINTEGRANT COMPOSITION FOR DISPERSIBLE SOLIDS			
(57) Abstract			
<p>A composition of matter useful as an excipient for increasing the disintegration rate of solid dosage forms of active agents in pharmaceutical, agricultural, industrial and like formulations wherein the excipient is a composition comprising a super disintegrant and a co-disintegrant.</p> <p>has:</p> <p>Ca Silicate</p> <p>MCC - binder</p> <p>superdis → cross linked polymer ↳ cross povidone</p> <p>active?</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

DISINTEGRANT COMPOSITION FOR DISPERSIBLE SOLIDS

5

Field Of The Invention

This invention relates to compositions and methods for preparing and using the same, which compositions are useful as rapid disintegrants for water-dispersible solid dosage forms of active agents. More particularly, this invention relates to compositions comprising super disintegrants and co-disintegrants useful as excipients for pharmaceutical, agricultural, food, industrial, household and like commercially useful active compounds in solid dosage form which desirably should disintegrate rapidly when placed in an aqueous environment. Compositions containing this novel disintegrant and an active agent, optionally with additives, is also encompassed by this invention.

Background Of The Invention

It is the common practice to manufacture solid dosage forms in which the ingredients, i.e., active agents, excipients, adjuvants, etc. are processed into various forms such as tablets, briquettes, pellets, granules, and the like. Among the more preferred excipients are the disintegrants, and particularly super disintegrants, such as croscarmellose or the like further described below. The solid dosage forms made with these super disintegrants are durable and stable yet readily disintegrate when added to an aqueous medium with concomitant release of the active components.

However, these super disintegrants are relatively expensive excipients. Consequently, their application has been confined largely to high cost items such as pharmaceutical tablets. They have not, for instance, proved economically feasible in preparing water-dispersible solid dosage forms of agricultural chemicals, e.g., insecticides, herbicides, fungicides, etc. which are of considerably lower per unit price than pharmaceuticals.

Therefore, it is an object of this invention to provide compositions combining a highly effective primary disintegrant (also referred to as super disintegrant) with a co-disintegrant compositions which are at least as effective as

super disintegrants but which are much less costly, in which the co-disintegrant synergizes the disintegrant properties of the primary disintegrant.

Representative of earlier efforts in this field are, for example U.S. Patent
5 4,744,987 (Mehra et al), directed to a blend of microcrystalline cellulose (MCC)
and calcium carbonate in pharmaceuticals; PCT publication WO 92/12633 (Mehra
et al), which discloses a combination of MCC and a nitrogenous compound; and
Japanese Application 81/022,839 (Japan Metals and Chemical Co.) which employs a
disintegrant comprising bentonite and an alkali metal silicate for agricultural
10 formulations.

Summary Of The Invention

It has now been discovered, in accordance with the present invention, that
15 the quantity super disintegrants necessary to rapidly disintegrate water-dispersible,
solid dosage forms containing active agents may be substantially reduced, while at
the same time maintaining or increasing the rate of disintegration, by substituting
for a portion of the super disintegrant a co-disintegrant comprising a diatomaceous
earth, a hydrophilic zeolite or a combination thereof to obtain a disintegration rate
20 at least equal to, but preferably greater than that of the super disintegrant alone.

Alternatively, in accordance with this invention, a disintegration rate
increase can be achieved by simply adding minor amounts of co-disintegrant to a
constant amount of super disintegrant. Substitution of the co-disintegrant for super
25 disintegrant, is, however, preferred.

It will be understood, however, that in many applications, particularly those
used in relatively low unit cost formulations such as in the agricultural field, a less-
than-optimum disintegration rate may be justified if there is a sufficient cost saving.
30 Thus, for each application the weight percent of co-disintegrant which may be
substituted for the more costly super disintegrants in this invention is not a fixed
range, but rather may be adjusted to optimize either cost or disintegration rate, or
both.

Generally, it has been found that the weight percent of the combined super disintegrant and co-disintegrant which may be used in the total weight of any formulation is about 0.05 wt.% to about 10 wt%, preferably about 0.5-3.0 wt.%, more preferably, about 1-3 wt%, depending on the nature of the active ingredients.

- 5 From these ranges it will thus be seen that the co-disintegrant alone, expressed as a weight percent of the total composition, may comprise from about 0.01 to 9.0 wt%, preferably about 0.1 to 2.7 wt%; and that the weight percent of the super disintegrant may comprise from about 0.045 to 8.0 wt%, preferably about 0.045 to 2.4 wt%.

10

- The weight ratio of super disintegrant to co-disintegrant in the disintegrant combination may range from about 4:1 to about 1:10, preferably 3:1 to 1:5, and most preferably about 2:1 to 1:1. That is to say, expressing it somewhat differently, as much as about 25 to 90 wt.%, preferably about 25 to 85 wt%, and
15 more preferably about 33 to 50 wt%, of the amount of super disintegrant *per se* which is necessary for sufficient disintegration may be replaced in the combination of this invention by co-disintegrant by virtue of this discovery.

DETAILED DESCRIPTION

20

The composition of the invention may readily be prepared by combining the super disintegrant with the co-disintegrant in any suitable manner for mixing particulate materials, including dry blending, granulation, or the like. Such mixing techniques are well known in the art.

25

- Solid formulations are then prepared by mixing the blended components with the desired active agent plus, if desired, any ancillary ingredients, and the resulting mixture processed to include the desired forms such as tablets, pellets, beads, granules, balls, bars, disks and briquettes. Wettable powders, which do not require
30 disintegrants, are excepted.

Thus, formulations may be produced from the blend of disintegrants and active agent by any of various known processes, including compression, roller compaction, wet granulation, extrusion, spheronization, and/or pan granulation.

5 When tableting is the method selected for producing the solids, conventional dry granulation, wet granulation, direct compression, spheronization or spray drying may be used to prepare the blend for tableting. The selection of method depends primarily on the active agent, the ability of the mixture of the disintegrants and active agent to flow freely in the tableting machine or extruder, and the
10 cohesiveness of the ingredients. If the active agent can be admixed with the disintegrants to produce a free flowing, dense powder, the mixture can be directly compressed. In dry granulation, a dry powdery blend of the components is compressed to form slugs if a tablet press is used. Alternatively, the dry blend is roller compacted into sheets. The slugs or sheets are then sieved to form densified
15 granules for final tableting.

 The hardness of the resulting tablet, granule, etc. can be determined routinely by the formulator depending upon the amount and type of additives employed and the degree of pressure in, e.g., the tableting machine. The degree of
20 hardness, may affect the disintegration rate, but as shown in Example 4 the increase in disintegration time is not greatly affected by increasing hardness. For example, tablets should be hard enough to resist chalking and/or breaking during normal handling but readily disintegrate in an aqueous medium.

25 The super disintegrants which may be employed in this invention, and which are well-known in the art, include such compounds as croscarmellose sodium (Ac-Di-Sol[®], FMC Corp., Philadelphia, PA.), crospovidone, sodium starch glycolate, and the like, or combinations thereof. See Handbook of Pharmaceutical Excipients, 2nd Ed., American Pharmaceutical Association, pp. 141 et seq. (1994). Of these,
30 croscarmellose sodium is preferred. Chemically, it will be seen that each of these compounds represents examples of a wholly or partially cross-linked compound such as a cross-linked cellulose or carboxymethyl cellulose, a cross-linked

polymer, and a cross-linked starch, respectively. Also, other alkali metal salts may be substituted for the sodium salts generally employed in these materials.

The co-disintegrant employed as the second component in the disintegrant composition of this invention are water-insoluble, but highly hydrophilic materials which include not only well-known natural diatomaceous silica (i.e., kieselguhr or infusorial earth), but also such materials as synthetic hydrous calcium silicate prepared by the hydrothermal reaction of natural diatomaceous silica and lime, in which the lime content may range from 20 to 50 wt. %, usually about 26 wt% (e.g., Micro-Cel[®], sold by Manville Corp., Denver Colo.) In addition to lime there may also be used magnesium compounds as well as other alkaline earth elements in the preparation of these synthetic materials. Of these silicas the synthetic calcium silicate is preferred. Other silica-containing materials, however, such as fumed silica clays, and like inorganic substances are excluded from the purview of the invention. The co-disintegrant may also be a hydrophilic zeolite, preferably one with large open pore structure for channeling of water into a compressed tablet. The co-disintegrant, it should be noted, as shown by the examples, should have minimal disintegrant properties when employed alone.

The active agents to be delivered with the disintegrants of the invention include any liquids adsorbed on appropriate solids, semi-solids or solid compounds, or mixtures of compounds which are to be eventually dispersed or dissolved in an aqueous medium including agricultural sprays, an industrial process or waste stream, a body of water such as a river or lake, a swimming pool, an oil well, a body fluid, an aqueous food, food supplement or pharmaceutical, or the like. Of course, the active agent must not be reactive with the properties of the blend. The solid forms of the invention, therefore, have application to a wide variety of fields and products, including agricultural and veterinary products, pharmaceuticals, animal and human foods, swimming pool additives, industrial biocides for oil wells and other applications, cosmetics, household pesticides, industrial and laundry detergents, and dye manufacturing.

The amount of active agent is not critical and thus can range broadly from about 10 to 95 wt% of the total composition, with the balance comprising the disintegrant of this invention plus, additives, adjuvants, etc., if any. Necessarily this amount may encompass e.g. materials ranging from pharmaceutical to agricultural materials, etc., plus necessary additives and adjuvants, and thus a large variation in amounts must be determined by those skilled in each different art. It follows from this, that the amount of disintegrant of this invention must also vary significantly depending on the nature and amount of said active agent and other additives and adjuvants, if any.

10

In the agricultural field, for example, the active agents include pesticides such as herbicides, insecticides, fungicides, plant growth regulators, fertilizers and biocides of all types. The pesticides include atrazine, benazone, bromoxynal, trifluralin, propanil, metribuzin, alachlor, butachlor, bromoxynil, clomazone, oxadiazon, lorsban, bifenox, aldicarb, monocrotophos, propoxur, diflubenzuron, carbofuran, permethrin, carbonyl, cypermethrin, endosulfan, cyfluthrin, bifenthrin, terbufos, fenamiphos, cadusafos, paclobutrazol, glyphosine, gibberellic acid, glycoposphate, phenylurea, and the like.

20

From these broad fields of use it follows that many other materials may be included as additives, adjuvants, etc. in the final solid composition as long as they do not interfere with the effectiveness of the active ingredient or disintegrant composition. Accordingly, those skilled in the formulations art will recognize that various ingredients well-known to formulators of solid forms can be added to the composition of the invention to enhance the blending, shaping and like processes. These include lubricants, glidants, dispersants, suspending agents, surfactants, and fillers or auxiliary binders, which are preferably employed in relatively small amounts, if any, i.e., from zero up to about 20% by weight of the total solid dosage form, more often less than about 10% by weight. However, this amount is not critical and may comprise as much as a major proportion by weight i.e., in excess of 50 wt% of the total formulation thus, in practice, the choice of additive and

25

30

amount are matters of routine consideration and trial for the skilled formulator, depending on the nature of the active agent.

For example, lubricants facilitate the ejection of compacted forms from a die cavity. They may also reduce interparticle friction and prevent adhesion of materials to die and punch surfaces. Typical lubricants are talc; long chain fatty acid esters or salts thereof such as stearic and palmitic acids, and magnesium or calcium stearate; and the like. Glidants are limited to improvement of the flow properties of powders and granules, and include materials such as aerogenic silica, fumed silicon dioxide and silica hydrogel.

There may also be included as disintegrants such compounds as guar gum, magnesium aluminum silicate, copolymers of methacrylic acid with divinylbenzene, potassium alginate, starch, and pregelatinized starch as additives to supplement the above super disintegrants.

Other additives which may be utilized include known binders/fillers as dicalcium phosphate, Starch 1500 (sold by National Starch Co., Bridgewater N.J.), lactose, and microcrystalline cellulose (MCC) compositions, for example, Lattice[®] NTC 70, (sold by FMC Corp., Philadelphia, Pa.) which, is a coprocessed blend of MCC and carboxymethyl cellulose or Lattice[®], NT 200, which is microcrystalline cellulose alone.

Dispersants may be employed to further break down disintegrated aggregates to primary particle size, and include such materials as naphthalene condensates, ligno-sulfonates, polyacrylates, and phosphate esters.

In the agricultural field particularly, the compounds are generally not applied full strength but are typically applied as formulations which may be applied as such or further diluted for application. Typical formulations include, for example, dust and granule compositions containing the active ingredient in combination with one or more agriculturally acceptable adjuvants, carriers or diluents, preferably with a surface active agent, and optionally with other active ingredients. The choice of

formulation depends, of course, on the type of pest and environmental factors present at the particular locus of infestation.

With due consideration to these factors, the active ingredient of a typical agricultural formulation may, for example, comprise 0.01 percent to 1 percent up to about 90 or 95 percent by weight, preferably 1 percent up to 90 or 95 percent by weight, of the formulation. Agriculturally acceptable carriers, diluents, adjuvants, surface active agents, and optionally other suitable active ingredients comprise the balance of the formulation. Thus a typical formulation may contain from 0.01 to 95 (preferably 1 to 95) percent by weight active ingredient, from 0 to 30 percent by weight surface active agent, and from 5 to 99.99 (preferably 5 to 99) percent by weight of an inert agriculturally acceptable carrier or diluent.

Granules, for agricultural use, for example, are solid or dry compositions of active ingredient compressed, deposited, or agglomerated to form large particles. Granules usually have an average particle size in the range of 150 to 5000 microns, typically 425 to 850 microns. Granular formulations generally contain from 1 to 50 percent by weight of one or more of the surface active agents described above, and from 50 to 98 percent by weight of one or more of the inert solid or dry carriers or diluents described above. Granules may be produced by agglomeration of dusts or powders, by compaction, by extrusion through a die, or by use of a granulation disk.

The novel compositions of this invention provide not only a rapid rate of disintegration of the solids at significant cost savings for super disintegrants, but also, particularly in the pharmaceutical field, flexibility in dosage form design. Furthermore, chemically incompatible actives, such as tablets containing several different pesticides or combinations of herbicides and pesticides, can be separated in the solid dosage forms by forming multilayers using known techniques.

The disintegrant composition of this invention may, as stated above, be incorporated into conventional pharmaceutical preparations such as tablets (e.g. compressed tablets which may be coated, as with sugar paste). In such preparations

the active agent may be present in admixture with a pharmacologically acceptable solid carrier; for example it may be a solid such as corn starch. The dosage to be employed may be determined by routine experimentation well known in the art. The active agent may be administered in combination with other drugs together with
5 the novel disintegrant excipient.

The following examples will further illustrate the invention without limiting the scope and spirit thereof, it being understood that the invention is entitled to the full scope and range of equivalents indicated in the appended claims.

10

In the following examples, Examples 1-7 show that synthetic, hydrous calcium silicate works effectively with croscarmellose sodium, sodium starch glycolate, and crospovidone three of the materials referred to above as 'super disintegrants', in increasing the disintegration rate. Example 8 illustrates that
15 comparable results may be obtained with natural diatomaceous earth. It will be noted that the combinations in the examples that included croscarmellose sodium were most effective.

Since diatomaceous materials used have been approved for pharmaceutical
20 formulations, examples 1 through 4 are representative of a vitamin formulation, such as niacinamide. Also, agricultural chemicals such as pesticides are frequently tableted to produce unit doses that need only to be placed in a specified volume of water prior to application. Example 5 is intended to exemplify the use of this disintegrant combination in an agricultural pesticide formulation, since ferrous
25 sulfate is listed as a selective herbicide to control broadleaf weeds. Industrial uses would include, for example, detergents such as are shown in examples 6 and 7, or granular fertilizers, which could be formulated routinely by those skilled in the art. Example 9 illustrates the use of a hydrophilic zeolite as a co-disintegrant.

30 In the examples, the additives include binders, such as microcrystalline cellulose, starch and/or lactose, lubricants such as magnesium stearate and/or stearic acid, and fillers such as dicalcium phosphate.

Example 1

In a twin cone blender (made by Patterson-Kelley Co., East Stroudsburg, Pa.) were combined 50 grams (25.0 wt %) of niacinamide, 140 grams (70 wt %) of dicalcium phosphate. 1.0 gram (0.5 wt %) of croscarmellose sodium (Ac-Di-Sol[®]) (sold by FMC Corporation, Philadelphia, PA 19103), 4.0 grams (2.0 wt %) of synthetic diatomaceous silica, and 4.0 grams (2.0 wt %) of stearic acid. All of these dry materials had been passed through a 30 mesh U. S. Standard screen prior to being placed in the blender. These components were blended for 10 minutes after which 1.0 gram (0.5 wt %) of magnesium stearate was added to the blender. Mixing was continued for an additional three minutes. The blended material was then compressed into tablets weighing 775 mg on a Stokes single station F press (made by Stokes-Merrill, Inc., Bristol, Pa.) fitted with 12.7 mm (0.5 inch) flat-faced, beveled-edge tooling. Twenty-four hours after compression, hardness was measured for six tablets. The median hardness of these tablets was 10.2 Kp (kiloponds). Also, disintegration tests were performed using USP 701 XXII apparatus. These tests were done in 37°C distilled water. The average disintegration time for six tablets was 1.3 ± 0.4 minutes as judged usually. For comparative purposes, a control formulation was prepared in which neither croscarmellose sodium nor synthetic diatomaceous silica was included.

Two other formulations were also prepared, one in which 1.0 gram (0.5 wt %) of croscarmellose sodium was included and the other in which 4.0 grams (2.0 wt %) of synthetic diatomaceous silica was included, but not both ingredients simultaneously. In all comparative formulations the amount of dicalcium phosphate was increased by the amount of diatomaceous silica and/or croscarmellose sodium which had been omitted. The tablets were measured for hardness and disintegration times in exactly the same manner as had been done for the tablets of this invention. In Table 1 the tablets of the invention are labeled 1a, those of the control 1b, those in which diatomaceous silica was omitted 1c, and those in which croscarmellose sodium was omitted 1d.

Table 1

Formulation	1a	1b	1c	1d
Ingredients	(Weight Percent)			
Niacinamide	25.0	25.0	25.0	25.0
Dicalcium phosphate	70.0	72.5	72.0	70.5
Croscarmellose sodium	0.5		0.5	
Diatomaceous silica	2.0			2.0
Stearic acid	2.0	2.0	2.0	2.0
Magnesium stearate	0.5	0.5	0.5	0.5
Tablet Properties				
Hardness (Kp)	10.2	10.5	10.1	10.1
Disintegration time (min)	1.3±0.4	25	4.7±0.2	25

Example 2

- 5 By the method of Example 1, 50 grams (25 wt %) of niacinamide, 140 grams (70 wt %) of dicalcium phosphate, 1.0 gram (0.5 wt %) of sodium starch glycolate, 4.0 grams (2.0 wt %) of synthetic diatomaceous silica, 4.0 grams (2.0 wt %) of stearic acid, and 1.0 gram (0.5 wt %) of magnesium stearate were combined and compressed into tablets weighing 775 mg. The properties of these tablets were
- 10 measured as described in Example 1. Table 2 shows the formulations corresponding to those in Table 1 with the sodium starch glycolate replacing croscarmellose sodium. Example 2a is a formulation of the invention, and Examples 2b-2d are comparative examples.

Table 2

Formulation	2a	2b	2c	2d
Ingredients	(Weight Percent)			
Niacinamide	25.0	25.0	25.0	25.0
Dicalcium phosphate	70.0	72.5	72.0	70.5
Sodium starch glycolate	0.5		0.5	
Diatomaceous silica	2.0			2.0
Stearic acid	2.0	2.0	2.0	2.0
Magnesium stearate	0.5	0.5	0.5	0.5
Tablet Properties				
Hardness (Kp)	10.8	10.5	11.2	10.1
Disintegration time (min)	18.3±4.8	25	23.0±3.4	25

Example 3

- 5 By the method of Example 1, 50 grams (25 wt %) of niacinamide, 140 grams (70 wt %) of dicalcium phosphate, 1.0 gram (0.5 wt %) of crospovidone, 4.0 grams (2.0 wt %) of synthetic diatomaceous silica, 4.0 grams (2.0 wt %) of stearic acid, and 1.0 gram (0.5 wt %) of magnesium stearate were combined and compressed into tablets weighing 775 mg. The properties of these tablets were
- 10 measured as described in Example 1. Table 3 shows the formulations corresponding to those in Table 1 with the crospovidone replacing croscarmellose sodium. Example 3a is a formulation of the invention, and Examples 3b-3d are comparative examples.

Table 3

Formulation	3a	3b	3c	3d
Ingredients	(Weight Percent)			
Niacinamide	25.0	25.0	25.0	25.0
Dicalcium phosphate	70.0	72.5	72.0	70.5
Crospovidone	0.5		0.5	
Diatomaceous silica	2.0			2.0
Stearic acid	2.0	2.0	2.0	2.0
Magnesium stearate	0.5	0.5	0.5	0.5
Tablet Properties				
Hardness (Kp)		10.5	10.7	10.1
Disintegration time (min)	2.9±0.4	25	4.3±1.8	25

Example 4

- 5 In a twin cone blender were combined 125 grams (25.0 wt %) of niacinamide, 350 grams (70 wt %) of dicalcium phosphate, 2.5 grams (0.5 wt %) of croscarmellose sodium, 10.0 grams (2.0 wt %) of synthetic diatomaceous silica, and 10.0 grams (2.0 wt %) of stearic acid. All of these dry materials had been passed through a 30 mesh U. S. Standard screen prior to being placed in the blender.
- 10 These components were blended for 10 minutes after which 2.5 grams (0.5 wt %) of magnesium stearate was added to the blender. Mixing was continued for an additional three minutes. The blended material was then compressed into tablets weighing 1750 mg on a Stokes single station F press fitted with 15.9 mm (0.625 inch) flat-faced, beveled-edge tooling. The compression forces were varied to
- 15 produce tablets having tablet hardness of 4, 8, and 12 Kp, respectively. Twenty-four hours after compression, hardness was measured for six tablets at each compression force. Also, disintegration tests were performed using USP 701 XXII apparatus. These tests were done in 37°C distilled water. The average disintegration time for six tablets at each hardness was determined.

For comparative purposes, a control formulation was prepared in which croscarmellose sodium was the only disintegrant incorporated. In the comparative formulation the amount of dicalcium phosphate was increased by the amount of synthetic diatomaceous silica that was omitted. Table 4 provides the composition of the two formulations and a summary of hardness and disintegration times for the tablets prepared from them. Example 4a is a formulation of the invention, and Example 4b is the comparative example.

Table 4

Formulation	4a	4b
	Weight	Weight
Ingredients	<u>Percent</u>	<u>Percent</u>
Niacinamide	25.0	25.0
Dicalcium phosphate	70.0	72.0
Croscarmellose sodium	0.5	0.5
Diatomaceous silica	2.0	
Stearic acid	2.0	2.0
Magnesium stearate	0.5	0.5
Tablet Properties	Hardness	Disintegration
	(Kp)	time (min)
	4.0	0.4
	8.0	1.1
	12.0	1.9
		Disintegration
		time (min)
		3.7
		7.6
		11.6

10

Example 5

In a twin cone mixer were placed 100 grams (50 wt %) of ferrous sulfate, 62 grams (31 wt %) of anhydrous lactose, 30 grams (15 wt %) of Starch 1500, 4 grams (2 wt %) of microcrystalline cellulose (Lattice™ NTC-70, sold by FMC Corporation, Philadelphia, PA), 2 grams (1 wt %) of sodium croscarmellose, and 2 grams (1 wt %) of synthetic diatomaceous silica. All of these dry materials had been passed through a 30 mesh U. S. standard screen prior to being placed in the blender. These dry ingredients were blended for 10

minutes after which they were placed in a 1.9 liter (2 quart) Hobart® planetary mixer. To the stirred dry mixture was added slowly 40 grams of distilled water. Since a homogenous semi-paste was not formed with this amount of water, additional water was added incrementally until the desired consistency was attained. A total of 78 grams (34 wt % of the dry formulation) of distilled water was required to obtain this consistency. The paste that was formed was then extruded through a 2.0 mm screen, and 35 grams of the extrudate was placed in a 15.2 cm (6 inch) spheronizer operated at one-half speed for three minutes to polish the product into uniform, dust-free granules. These granules were then dried in an oven at 60°C for 120 minutes, resulting in a residual moisture below 5%. The granule sizes ranged from 425-1180 microns. These granules were described as being very durable. The disintegration time of the granules was determined by the method of USP 701 XXII using a 100 mesh screen. A 5 gram sample of the granules was placed in the basket which was immersed in 37°C distilled water. The disintegration time of this sample was 1.1 minutes. This description is specific to Example 5a, but the same procedure was followed for Examples 5b-5d. Table 5 shows the formulations corresponding to those in Table 1, i.e. Example 5a is an example of the invention, and Examples 5b-5d are comparative examples.

Table 5

Formulation	5a	5b	5c	5d
Ingredients	(Weight Percent)			
Ferrous sulfate	50	50	50	50
Lactose (anhydrous)	31	33	31	31
Starch 1500 ^{TM a)}	15	15	15	15
Lattice NTC-70 ^{TMb)}	2	2	2	2
Croscarmellose sodium	1		2	
Diatomaceous silica	1			2
Water of granulation (%)	34	28	46	34
Granule Property				
Disintegration time (min)	1.1	5.9	2.6	3.8

a) National Starch and Chemical Co., Bridgewater, N.J.

b) Microcrystalline cellulose in carboxymethyl cellulose (FMC Corp., Phila, PA.)

Example 6

In a twin-cone blender were combined 133.2 grams (66.6 wt %) of Alconox[®] Detergent powder (Alconox, Inc., New York, NY 10003), an alkaline detergent comprising a blend of sulfates, phosphates, and carbonates, and used, e.g., as a laboratory equipment cleaner, 60 grams (30.0 wt %) of Lattice[™] NT200 (FMC Corporation, Philadelphia, PA 19103), 3.0 grams (1.5 wt %) of croscarmellose sodium (Ac-Di-Sol[®] sold by FMC Corporation, Philadelphia, PA 19103), 3.0 grams (1.5 wt %) of synthetic diatomaceous silica, and 0.8 gram (0.4 wt %) of magnesium stearate. All of these dry materials had been passed through a 30 mesh U. S. Standard screen prior to being placed in the blender. These components were blended for 5 minutes. The blended material was then compressed into tablets weighing 3 grams on a Stokes single station F press fitted with 19.05 mm (0.75 inch) flat-faced, beveled-edge tooling. The compression forces applied were sufficient to produce tablets having a hardness of approximately 5 Kp. Twenty-four hours after compression, hardness was measured for six tablets. Also disintegration

tests were performed using USP 701 XXII apparatus. These tests were done in 21°C distilled water. The average disintegration time for six tablets was determined. For comparative purposes, control formulations were prepared in which no excipient was added; one in which only Lattice NT200 was included; one in which only synthetic diatomaceous silica was in combination with Lattice NT200; and one in which croscarmellose sodium was in combination with Lattice NT200. In the comparative formulations the amount of Alconox detergent powder was adjusted to make up for the added excipients. The comparative examples are numbered 6a, 6b, 6c, and 6g, respectively. Table 6 provides the composition of all formulations and a summary of hardness and disintegration times for the tablets prepared from them. Examples 6d, 6e, and 6f are all examples of the invention; however, Example 6e is the specific formulation of the invention that is described in this example. All examples were prepared by the identical method, adjusting the amounts of each component appropriately.

15

Example Ingredient	Table 6						
	6a	6b	6c	6d	6e	6f	6g
Weight Percent							
Alconox	99.6	69.6	66.6	66.6	66.6	66.6	66.6
Microcrystalline cellulose ^a		30.0	30.0	30.0	30.0	30.0	30.0
Croscarmellose sodium			-	0.75	1.5	2.25	3.0
Diatomaceous silica			3.0	2.25	1.5	0.75	-
Magnesium silicate	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Tablet properties							
Hardness (Kp)	5.4	4.9	4.7	5.0	4.9	4.9	4.8
Disintegration time (seconds)	> 1800	330	127	81	47	101	103

^a Lattice NT200, FMC Corporation, Philadelphia, PA 19103

^b Synthetic diatomaceous silica.

Example 7

- By the method of Example 6, 136.2 grams (68.1 wt %) of Alconox³
- 5 Detergent powder (Alconox, Inc., New York, NY 10003), 60 grams (30.0 wt %) of Lattice™ NT200, 1.5 grams (0.75 wt %) of croscarmellose sodium (Ac-Di-Sol⁴), 1.5 grams (0.75 wt %) of synthetic diatomaceous silica, and 0.8 gram (0.4 wt %) of magnesium stearate were mixed in a twin cone blender. Tablets weighing approximately 3.0 grams were compressed in the same manner as described in
- 10 Example 6. The same testing procedures were also used. This specific example is identified as 7a, and the results for this example as well as two comparative examples, 7b and 7c, are shown in Table 7.

Ingredient	Table 7		
	7a	7b	7c
Weight Percent			
Alconox	68.1	68.1	68.1
Microcrystalline cellulose ^a	30.0	30.0	30.0
Croscarmellose sodium	0.75	1.5	-
Diatomaceous silica ^b	0.75	-	1.5
Magnesium stearate	0.4	0.4	0.4
Tablet properties			
Hardness (Kp)	5.0	5.2	5.2
Disintegration time (seconds)	147	222	288

- 15 ^a Lattice NT200, FMC Corporation, Philadelphia, PA 19103
- ^b Synthetic diatomaceous silica.

Example 8

- 20 By the method of Example 6, 133.2 grams (66.6 wt %) of Alconox³ Detergent powder 60 grams (30.0 wt %) of Lattice™ NT200, 3.0 grams (1.5 wt %) of croscarmellose sodium (Ac-Di-Sol⁴), 3.0 grams (1.5 wt %) of natural diatomaceous silica, and 0.8 gram (0.4 wt %) of magnesium stearate were mixed in a twin cone blender. Tablets weighing approximately 3.0 grams were compressed
- 25 in the same manner as described in Example 6. The same testing procedures were

also used. This specific example of the invention is identified as 8a. The results for this example as well as comparative examples 6g, 8b, and 8c are shown in Table 8.

Table 8

Ingredient	6g	8a	8b	8c
	Weight Percent			
Alconox	66.6	66.6	66.6	68.1
Microcrystalline cellulose ^a	30.0	30.0	30.0	30.0
Croscarmellose sodium	3.0	1.5	-	-
Diatomaceous silica ^b	-	1.5	3.0	1.5
Magnesium stearate	0.4	0.4	0.4	0.4
Tablet properties				
Hardness (Kp)	4.8	4.9	4.7	5.1
Disintegration time (seconds)	103	138	178	329

^a Lattice NT200, FMC Corporation, Philadelphia, PA 19103

^b Natural diatomaceous silica.

Example 9

10 In a twin cone blender were combined 173.2 grams (86.6 wt. %) of automatic dishwashing detergent powder (an alkaline detergent comprising a blend of sulfates, citrates and carbonates), 20.0 grams (10.0 wt. %) Lattice™ NT200, 3.0 grams (1.5 wt. %) modified cellulose gum (Accelerate DS812, sold by FMC Corporation, Philadelphia, PA 19103) and 0.8 gram (0.4 wt. %) magnesium
15 stearate. Co-disintegrants were then added by blending 3.0 grams (1.5 wt. %) of each test additive (synthetic diatomaceous silica, zeolite). All of these dry materials had been passed through a 30 mesh U.S. standard screen prior to being placed in the blender. These components were blended for 5 minutes. The blended material was then compressed into tablets weighing 3 grams on a Stokes single
20 station F press fitted with 19.0 mm (0.75 inch) flat faced, beveled edge tooling.

- The compression forces applied were sufficient to produce tablets having a hardness of approximately 6 Kp. Twenty-four hours after compression, hardness was measured for six tablets. Also disintegration tests were done in 21°C distilled water. The average disintegration time for six tablets was determined. This is
- 5 Example 9a in Table 9. For comparative purposes, control formulations were prepared in which no excipient was added; one in which only synthetic diatomaceous silica was added; one in which only zeolite was added. In the control formulation the amount of detergent powder was adjusted to make up for the excipients, which were excluded. Table 9 provides the composition of all
- 10 formulations and a summary of hardness and disintegration times for the tablets prepared from them. Examples 9a and 9b are examples of the invention. Example 9c is included in Table 9 for comparison.

Table 9

15

Formulation	9a	9b	9c
Automatic dishwashing powder [®]	86.6	86.6	86.6
Lattice [™] NT 200	10.0	10.0	10.0
Modified cellulose gum	1.5	1.5	3.0
Diatomaceous silica	1.5		
Zeolite		1.5	
Magnesium stearate	0.4	0.4	0.4
Tablet properties			
Hardness (Kp):	6.4 ± 0.2	6.0 ± 1.1	6.8 ± 0.3
Disintegration time (minutes):	4.1 ± 1.2	5.8 ± 1.0	9.8 ± 0.9

- From the above illustrations it will be seen most clearly that (i) in all the examples, the combination of a super disintegrant and a diatomaceous earth results in a faster disintegration rate than a super disintegrant alone; (ii) Examples 1-3,
- 20 with their greater than 25-minute disintegration time, show that diatomaceous earth alone does not act as an effective disintegrant, yet when added to a super disintegrant it increases the rate of the latter; (iii) this is particularly true of the combination of croscarmellose sodium and synthetic diatomaceous silica of Example 4, where, despite increasing hardness of the tablets tested, the disintegration time is

not increased greatly, and indeed is improved with one combination (4a), as much as four-fold; and (iv) as shown by Example 5, the reduction of the amount of more costly super disintegrant and its replacement with less expensive diatomaceous earth (5a) nevertheless resulted in a significant improvement in the disintegration rate
5 over the use of double the amount of super disintegrant alone (5c).

In Example 6, it will be seen that in Examples 6(d), 6(e), and 6(f), where the disintegrants are combined in accordance with this invention, (where 6(e) represents the specific formulation of the invention that is described in Example 6) the disintegration rate is superior to that of any of the control examples; (a), (b), (f),
10 and (g). This is especially evident in Examples 6(e) and (c), where increased amounts of diatomaceous silica are substituted for the super disintegrant. In Example 7 this improvement is also demonstrated, especially in view of one of the disintegration rates in Example 7(a), of the invention, which is about half that of the control examples. In Example 8a, it will be seen that the combination of super
15 disintegrant with natural diatomaceous earth is effective over diatomaceous silica alone.

CLAIMS

1. A composition useful as an excipient for active agents in solid dosage forms which comprises a super disintegrant and a co-disintegrant comprising
5 diatomaceous earth or a porous hydrophilic zeolite in amount sufficient to provide rapid disintegration of the solid form when placed in solution.

2. The composition of claim 1 wherein the super disintegrant is a wholly or partially cross linked compound selected from cross linked cellulose or carboxymethyl cellulose, a cross linked polymer and a cross linked starch.

10

3. The composition of claim 1 wherein the super disintegrant is croscarmellose alkali metal salt, crospovidone, alkali metal starch glycolate, or cross linked alkali metal carboxymethyl cellulose.

15

4. The composition of claim 1 wherein the co-disintegrant is natural diatomaceous silica.

5. The composition of claim 1 wherein the co-disintegrant is a synthetic hydrous alkaline earth metal calcium silicate.

20

6. The composition of claim 1 wherein the co-disintegrant is a porous hydrophilic zeolite.

7. The composition of claim 1 wherein the weight ratio of super
25 disintegrant to co-disintegrant is from about 4:1 to 1:10.

8. The composition of claim 1 wherein the weight ratio of super disintegrant to co-disintegrant is from about 3:1 to 1:5.

30

9. The composition of claim 1 wherein the weight ratio of super disintegrant to co-disintegrant is from about 2:1 to 1:1.

10. The composition of claim 1 wherein about 20 to 90 wt% of the disintegrant composition is composed of the co-disintegrant.

35

11. A solid dosage form comprising the composition of claim 1 and further comprising an active agent.

12. The composition of claim 11 wherein the combined super disintegrant and co-disintegrant of claim 1 comprise from about 0.05 to about 10 wt% of the total composition.

13. The composition of claim 11 wherein about 20 to 90 wt% of the super disintegrant is replaced by the co-disintegrant.

10

14. The composition of claim 11 wherein the active agent is an agriculturally active compound.

15. The composition of claim 11 wherein the active agent is a pharmaceutical active compound.

16. The composition of claim 11 wherein the active agent is a detergent.

17. The composition of claim 9 wherein the active agent comprises from about 10 to 95 wt% of the total dosage form.

18. The composition of claim 11 further comprising one or more suitable excipients, additives and adjuvants for the active agent.

19. The composition of claim 18 wherein the excipients, additives and adjuvants are selected from glidants, lubricants, dispersants, suspending agents, surfactants, or mixtures thereof.

20. The composition of claim 19 wherein the excipients, additives, and adjuvants comprise as much as a major percent by weight of the total composition.

AMENDED CLAIMS

[received by the International Bureau on 5 December 1997 (05.12.97);
original claim 1 amended; remaining claims unchanged (1 page)]

1. A composition useful as an excipient for active agents in solid dosage forms which comprises a super disintegrant and a co-disintegrant comprising diatomaceous earth, calcium silicate or a porous hydrophilic zeolite in amount sufficient to provide rapid disintegration of the solid form when placed in solution.
2. The composition of claim 1 wherein the super disintegrant is a wholly or partially cross linked compound selected from cross linked cellulose or carboxymethyl cellulose, a cross linked polymer and a cross linked starch.
3. The composition of claim 1 wherein the super disintegrant is croscarmellose alkali metal salt, crospovidone, alkali metal starch glycolate, or cross linked alkali metal carboxymethyl cellulose.
4. The composition of claim 1 wherein the co-disintegrant is natural diatomaceous silica.
5. The composition of claim 1 wherein the co-disintegrant is a synthetic hydrous alkaline earth metal calcium silicate.
6. The composition of claim 1 wherein the co-disintegrant is a porous hydrophilic zeolite.
7. The composition of claim 1 wherein the weight ratio of super disintegrant to co-disintegrant is from about 4: 1 to 1: 1 0.
8. The composition of claim 1 wherein the weight ratio of super disintegrant to co-disintegrant is from about 3:1 to 1:5.
9. The composition of claim 1 wherein the weight ratio of super disintegrant to co-disintegrant is from about 2: 1 to 1: 1.
10. The composition of claim 1 wherein about 20 to 90 wt% of the disintegrant composition is composed of the co-disintegrant.

STATEMENT UNDER ARTICLE 19

Claim 1 has been amended to correspond to the pending U.S. patent application. No new matter has been added.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12183

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A01N 25/08, 25/12; A61K 9/14

US CL : 424/409, 421, 485, 490, 493

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/408, 409, 413, 419, 421, 485, 493

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,780,315 A (WU et al.) 25 October 1988, see columns 5 and 6, examples 6 and 20.	1-3, 6-11, 13-15, 17-20 ----- 1-11, 13-20
Y	US 5,074,902 A (CONNICK, JR. et al.) 24 December 1991, see entire document	1-11, 13-20
Y	US 5,314,852 A (KLATTE) 24 May 1994, see entire document.	1-11, 13-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

10 SEPTEMBER 1997

Date of mailing of the international search report

06 NOV 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

NEIL LEVY *IW for*

Telephone No. (703) 308-2351

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12183

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 12
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.